

REMARKS

A. Status of the Application

Claims 1-13 were pending at the time of the last Office Action. Claims 1, 3-5, and 13 have been amended. No claims have been added. Claim 10 has been cancelled. Therefore, claims 1-9, and 11-13 remain pending. No new matter has been added.

B. Section 112 Enablement Rejections

Claims 1-13 stand rejected under 35 U.S.C. § 112, first paragraph for allegedly lacking enablement. The Office asserts that the Specification lacks enablement “for a method wherein gene expression profiles are classified for false/potential/real positives without reciting specific trait, disease, tissue, and/or criterium/standard for classifying as positives.” May 2006 Office Action at page 3. The Office concludes that: “[d]ue to the undue experimentation required to obtain the goal of the invention in the absence of any recited trait, disease, or disorder, the lack of directions presented in the specification for how to do so, . . . the specification fails to teach to teach one skilled in the art how to use the claimed method for associative analysis.” *Id.* at page 4. The Office’s conclusion is based on analysis that incorrectly interprets the claims, and particularly the classification step. *See id.* at pages 2-4. Applicants respectfully traverse.

1. The Specification Fully Discloses Classifying Differentially Expressed Genes as False/Real/Potentially Real Positives with Respect to the Control Group

The Office asserts that the classification of differentially expressed genes requires knowledge of a particular “trend,” trait, or disease that is not disclosed in the specification.

The instant specification does not provide specific guidance to practice the invention because it does not disclose how to classify differentially expressed genes as false/real positive without knowing a trait, stage of tissue, and/or disease associated with the gene expression. Without knowing for what “trend” genes are classified as positives, the associative analysis would require undue experimentation.

May 2006 Office Action at page 3. The Office states that “[p]rior art analysis shows that classifying the differentially expressed genes as positives/negatives requires knowledge of a trait and/or disease.” *Id.*

The Office’s analysis misstates the recited step of “classifying,” and the current rejection is therefore not justified. As amended, independent claim 1 states in relevant part:

collecting a plurality of expression profiles of a control group and a plurality of expression profiles of an experimental group . . .

identifying a group of similarly expressed genes, defining a reference group, determined from the plurality of expression profiles of the control group;

identifying a plurality of differentially expressed genes in the plurality of expression profiles of the experimental group based on the reference group, wherein identifying the plurality of differentially expressed genes comprises utilizing a paired T-test and an associative T-test; and

classifying the differentially expressed genes as (a) likely false positive, (b) real positives, or (c) potential positives using the paired T-test and associate T-test, wherein classifying comprises:

classifying the genes identified as expressed by the paired T-test and not identified as expressed by the associative T-test as false positives;

classifying the genes identified as expressed by the paired T-test and the associative T-test as real positives; and

classifying the genes identified as expressed by the associative T-test and not identified as expressed by the paired T-test as potentially real positives.

(Emphasis added.) Independent claim 13 is of different scope but recites similar limitations with respect to the enablement arguments. Examples of “classifying” are disclosed in the “Summary of the Invention” section of the Specification:

Classifying can include: (a) classifying the genes identified as expressed by the paired T-test as false positive; (b) classifying the genes identified as expressed by the paired T-test and the associative T-test as real positives; and (c) classifying the genes identified as expressed by the associative T-test as potentially real positives.

Application at page 6. Examples of “Classifying” are also discussed in detail in the “Detailed Description” section of the Specification:

(d) Comparing the selections from the paired T-test and associative T-tests to classify the differentially expressed genes as: (a) likely false positives (these are genes selected as differentially expressed by the paired T-test with $p < 0.05$, but not by the associative T-test); (b) real positives (selected in both tests) (c) potential positives (genes selected in the associative test only).

Id. at page 11.

Amended independent claims 1 and 13 clearly recite specific aspects of “classifying.” The claims explicitly recite the circumstances under which a classification of false positive, real

positive, or potentially real positive is made. Classification is “general” because it is based on a reference group determined from a control group, as claimed.

The claims are fully supported and enabled. For example, the Specification discloses how a paired T-test and associative T-test may be utilized to identify differentially expressed genes from an experimental group based on a reference group. *See id.* at page 4-5. *See id.* at pages 10-11. The Specification also enables the process for determining the experimental group and the reference group from a plurality of expression profiles. *See id.* at page 4, lines 12-20. *See id.* at pages 9-10. Therefore, the Specification fully discloses and enables classifying differentially expressed genes as false/real/potentially real positives in a general manner, through use of a reference group determined from a control group. Contrary to the Office’s assertion, no additional knowledge of a trait, disease, or trend is required to practice the invention.

2. The Specification Enables a “General” Classification of Differentially Expressed Genes with Respect to the Control Group

The Office asserts that “the specification does not teach a ‘general’ classification of expressed genes as false/real positives without knowing a trait/disease.” May 2006 Office Action at page 4. The Office’s assertion is based upon the same misinterpretation of the claims as discussed above. As previously discussed, the claims explicitly recite a general classification scheme, which is fully enabled.

3. Practice of the Claimed Invention Does Not Require Undue Experimentation

The Office asserts that the claims lack enablement because undue experimentation is required to practice the invention. The Office contends that “[i]n order to practice the claimed invention, one skilled in the art must randomly select a trait, disease, disorder, state of tissue, *etc.*, for which the differentially expressed genes are classified as positives.” May 2006 Office Action at page 4.

Applicants traverse. As previously discussed, the claims explicitly recite a general classification scheme, which is fully enabled. No random selection of a trait, disease, disorder, or state of tissue is required to practice the disclosed invention.

One of ordinary skill in the art would understand that embodiments of the Specification and the Claims are directed toward a statistical analysis wherein “classifying” of the differentially expressed genes as false positive, real positive, or potential positive is performed in

relation to a reference group, and that the reference group is determined from expression profiles of the control group. The disclosure fully enables the artisan of ordinary skill how to make and use the claimed invention without the need for undue experimentation. Accordingly, Applicants respectfully submit that the claims are properly enabled and the rejection should be withdrawn.

B. Section 112 Indefiniteness Rejections

Claims 1-13 stand rejected under 35 U.S.C. § 112, second paragraph for allegedly being indefinite for failing to point out and distinctly claim the subject matter. The Office states that it is unclear whether “to identify outlier” and “to re-scale to an average profile” are active, positive steps of the claimed method. The Office notes that the limitations are not recited in active voice. *See* May 2006 Office Action at page 5.

Applicants respectfully submit that claims 1-13 in their original form comply with the requirements of 35 U.S.C. § 112, second paragraph when read with the Specification. However, in the interest of furthering prosecution of this case, independent claims 1 and 13 are amended to address the Office’s rejection. Dependent claims 3-5 are amended to accommodate the revised language of claim 1.

Claim 1 and 13 are amended to recite the limitations “identifying outliers” and “re-scaling the plurality of expression profiles” in active voice. Accordingly, the basis for rejection is overcome. Reconsideration and withdrawal of this rejection is respectfully requested.

C. Section 102 Rejections

Claims 1, 3-5, 8-9, and 12 stand rejected under 35 U.S.C. § 102 for allegedly being anticipated by Xiao, BMC Genomics, 3:28 (27 Sept. 2002). *See* May 2006 Office Action at pages 5-6.

Applicants believe that Xiao fails to anticipate the present invention. For example, Xiao does not disclose the limitation of claim 1:

classifying the differentially expressed genes as (a) likely false positive, (b) real positives, or (c) potential positives using the paired T-test and associate T-test

Additionally, Applicants are providing a declaration under 37 C.F.R. §1.131 (“Rule 1.131 Declaration”) behind Tab A establishing that the subject matter of claims 1-13 was invented before the date of publication of the Xiao article, namely, September 27, 2002. The Rule 1.131 Declaration includes Applicants’ Bioinformatics article (published January 22, 2003) as evidence of prior invention. The article bears a revision date of May 27, 2002, which is prior to

publication date of the Xiao article. Accordingly, the Xiao article is not prior art under 35 U.S.C. § 102(a). Reconsideration and withdrawal of the rejection is therefore respectfully requested.

D. Section 103 Rejections

1. Claims 1-4, 8-9, and 12 are Patentably Distinct

Claims 1-4, 8-9, and 12 stand rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over Dozmorov, *J. Gerontol.*, 57A(3):B99-B108 (March 2002) in view of U.S. Publication No.: 2002/0072484 to Alters *et al.* The Office has maintained the rejection originally made in the Office Action mailed on November 2, 2005. Applicants respectfully traverse.

The Office has failed to establish a prima facie case of obviousness. A proper prima facie case requires that “the prior art reference (or references when combined) must teach or suggest all the claim limitations.” MPEP §2142. In this case, the combination of the references cited by the Office fails to teach or suggest all the elements of independent claim 1. For example, the combined references do not teach or suggest classifying the differentially expressed genes as (a) likely false positive, (b) real positives, or (c) potential positives using the paired T-test and associate T-test. . . .”

As claimed, “classifying” requires utilization of both a paired T-test and an associative T-test to determine whether the differentially expressed gene is classified as likely false positive, real positive, or potential positive. Additionally the claims explicitly point out how classification is made based on the specific results of those tests—a feature notably absent from all the cited art.

a. Neither Dozmorov nor Alters Discloses Classifying as Likely False Positive, Real Positive, or Potential Positive

The Office cites the Dozmorov publication as disclosing “classifying expressed genes as false positive using a t-test (*e.g.*, false discovery rate, type I and type II error, p. B101, left col. and p. B102, right col.).” November 2005 Office Action at page 5. However, the relevant claim limitation is “classifying the differentially expressed genes as (a) likely false positive, (b) real positives, or (c) potential positives using the paired T-test and associate T-test. . . .” The material cited by the Office is directed to the assessment of statistical significance of experimental data. *See* Dozmorov at p. B101. Calculation of p-value and probability of false positive results are discussed. *Id.* There is no teaching or suggestion of classification as claimed. Further, there is

no teaching or suggestion of the categories of “likely false positive,” and “potential positive.” Therefore, the Dozmorov publication does not provide disclosure for classifying differentially expressed genes as likely false positive, real positives, or potential positives.

The Alters reference is also silent to any teaching or suggestion of “classifying the differentially expressed genes as (a) likely false positive, (b) real positives, or (c) potential positives” Alters generally provides techniques for administering a drug to a subject, measuring a value of a biomarker, and comparing the measured value to a standard level. *See* Summary of the Invention, particularly [0015] and [0016]. Depending on the difference between the measured value of the inventive biological markers and the standard level, the effectiveness of the drug is analyzed. *See id.* Alters lacks any disclosure for classifying differential expressed genes, among other differences.

b. Neither Dozmorov nor Alters Discloses Classifying Using Both a Paired T-test and an Associative T-test

The Office admits that the Dozmorov publication fails to disclose a paired T-test and an associative T-test, but contends that the Alters reference cures this deficiency. November 2005 Office Action at page 6. The Office states that Alters discloses paired t-tests and “t-test comparing the entire population (associative t-test).” The Office concludes that it would be obvious to “modify the method of Dozmorov to use various t-test, such as those taught by Alters” *Id.*

The relevant limitation requires utilizing both a paired T-test and an associative T-test. Claim 1 is amended to clearly recite aspects of classifying using both the paired T-test and associate T-test, and states in relevant part:

classifying the differentially expressed genes as (a) likely false positive, (b) real positives, or (c) potential positives using the paired T-test *and* associate T-test, wherein classifying comprises:

classifying the genes identified as expressed by the paired T-test and not identified as expressed by the associative T-test as false positives;

classifying the genes identified as expressed by the paired T-test and the associative T-test as real positives; and

classifying the genes identified as expressed by the associative T-test and not identified as expressed by the paired T-test as potentially real positives.

Alters fails to teach or suggest classifying utilizing both tests in this manner, and thus the Alters reference does not disclose the relevant limitation. Also lacking is any discussion that would provide the artisan of ordinary skill motivation to combine the individual tests described in Alters into the utilization of both a paired T-test and associative T-test.

Additionally, the cited references fail to disclose or suggest how specific results of tests could be translated into classification categories, as claimed. Looking at claim 1 as an example, a false positive classification results for genes identified as expressed by the paired T-test **and not** identified as expressed by the associative T-test. Other explicit, specific test scenarios are called out for the other classifications within the claims. Dozmorov and Alters are silent to such features.

For at least the above reasons, independent claim 1 and its respective dependent claims are patentably distinct over the Dozmorov publication in view of the Alters reference. Applicants respectfully request the withdrawal of the § 103(a) rejection to claims 1-4, 8-9, and 12.

2. Claims 5-7 are Patentably Distinct

Claims 5-7 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the Dozmorov publication in view of the Alters reference in further view of the Thomas Wu publication entitled "Analysing Gene Expression Data from DNA Microarrays to Identify Candidate Genes." Applicants respectfully traverse.

As noted above, the Dozmorov publication in combination with the Alters reference fails to teach the or suggest the elements of independent claim 1. Similarly, the Wu publication is silent to any teachings or suggestions for, *e.g.*, classifying the differentially expressed genes as (a) likely false positive, (b) real positives, or (c) potential positives using the paired T-test and associate T-test, as recited in claim 1.

The Wu reference discloses surveys of analytical methods for gene-filtering tasks. *See* Abstract. In one respect, Wu discloses ranking genes based on their similarity to a given expression profile by "categorizing genes into two groups: those that are similar and those that are dissimilar to a given profile." *See* ¶1 of the section entitled "Supervised pattern recognition." Among other differences, this technique does not constitute classifying the differentially expressed genes as (a) likely false positive, (b) real positives, or (c) potential positives using the paired T-test and associate T-test, as recited in claim 1.

Therefore, the Wu publication, the Alters reference, and the Dozmorov publication, either separately or combined, do not teach or suggest all the elements of claim 1. Claims 5-7 are dependent claims of claim 1 and are patentably distinct over Wu and/or Alters for at least the same reasons. Applicants respectfully request the removal of the § 103 rejections.

PETITION FOR EXTENSION OF TIME

Pursuant to 37 C.F.R. § 1.136(a), Applicant petitions for a two-month extension of time, bringing the due date for this response to October 5, 2006. If no check is included to cover this process fee, or if any additional fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason relating to the enclosed materials, or should an overpayment be included, the Office is authorized to deduct or credit the appropriate fees from or to Fulbright & Jaworski Deposit Account No.: 50-1212/ OMRf:013US.

CONCLUSION

Applicants believe that these remarks fully respond to all outstanding matters for this application. Applicants respectfully request that the rejections of all claims be withdrawn so the claims may swiftly pass to issuance.

Should the Examiner desire to sustain any of the rejections discussed in this Response, the courtesy of a telephone conference between the Examiner, the Examiner's supervisor, and the undersigned agent at 512-536-3027 is respectfully requested in advance.

Respectfully submitted,



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TAB A